Transparencies from Meeting: Developmental and Reproductive Toxicity Identification Committee

July 27, 1998

A meeting of the Developmental and Reproductive Toxicity Identification Committee was held on July 27, 1998, at the 714 P Street, auditorium in Sacramento, California. Below are the transparencies of presentations made by staff of California Environmental Protection Agency's Office of Environmental Health Hazard Assessment (OEHHA). The segments of the agenda covered with this material include the "Authoritative Bodies Designations and Regulatory Criteria", "Existing Authoritative Bodies", and "Bodies Suggested by the Public for Designation as 'Authoritative'".

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Agenda
Meeting of the Developmental and Reproductive Toxicant (DART) Identification Committee

July 27, 1998
714 P Street, Auditorium, Sacramento

Meeting Chair: Andrew Hendrickx, Chair, DART Identification Committee

10:00 **Welcome**
Joan E. Denton, Director, Office of Environmental Health Hazard Assessment (OEHHA)

Introductory remarks and report on June 11th authoritative bodies workshop
Chairman Hendrickx and DART Committee

Background
Legal aspects
Ed Weil, Deputy Attorney General
Colleen Murphy, OEHHA Chief Counsel
Authoritative bodies designations and regulatory criteria
Lauren Zeise, OEHHA Reproductive and Cancer Hazard Assessment Section (RCHAS)

11:00 **Existing authoritative bodies (12:00 lunch)**

US Environmental Protection Agency
Staff presentations
Martha Sandy and Jim Donald, OEHHA RCHAS
Public comment
Committee discussion and decisions*****

National Institute of Occupational Safety and Health
Staff presentations
Martha Sandy and Jim Donald, OEHHA RCHAS
Public comment
Committee discussion and decisions*****

National Toxicology Program
Staff presentations
Martha Sandy and Jim Donald, OEHHA RCHAS
Public comment
Committee discussion and decisions*****

Existing authoritative bodies (continued)

International Agency for Research on Cancer
Staff presentations
Martha Sandy and Jim Donald, OEHHA RCHAS
Public comment
Committee discussion and decisions*****

Food and Drug Administration
Staff presentations
Martha Sandy and Jim Donald, OEHHA RCHAS
Public comment
Committee discussion and decisions*****

3:00 **Bodies suggested by the public for designation as "authoritative":**
US Agency for Toxic Substances and Disease Registry
International Programme for Chemical Safety
Health Canada / Environment Canada
Staff presentation
Jim Donald, OEHHA RCHAS
Public comment
Committee discussion*****

Additional Public Comment
Further Committee Discussion

5:00 **Adjourn**

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***** The Committee may take action on this item.

Proposition 65 Statute

"A chemical is known to the state to cause cancer or reproductive toxicity if ...

in the opinion of the state's qualified experts is has been clearly shown ... to cause cancer or reproductive toxicity, or

a body considered to be authoritative by such experts has formally identified it as causing cancer or reproductive toxicity, or

an agency of the state or federal government has formally required it to be labeled or as causing cancer or reproductive toxicity"

(added to Health and Safety Code by 1986 General Election)

California Code of Regulations
Title 22

12305 (b) "...the DART Committee may undertake the following activities:

"...(2) Identify bodies which considered to be authoritative and which have formally identified reproductive toxicants."

12306 (b) "The DART Committee ... shall have the authority to revoke or rescind any determination that a body is authoritative on the grounds that the ... Committee no longer considers the body to have expertise in the identification of chemicals as causing …reproductive toxicity..."

12306 Criteria an Authoritative Body Must Meet

1 It must be an agency or formally organized group

2 It must use a method to identify chemicals as causing cancer or reproductive toxicity provided in the Title 22 regulation

3 The State's qualified experts identify the body as having expertise in the identification of chemicals as causing cancer or reproductive toxicity

Authoritative Body Criteria

Chemical is "formally identified"

Requires satisfying criteria for

1 identification

2 formality

Identification Criteria:

The chemical is ...

- On a list of chemicals as causing reproductive toxicity issued by the authoritative body

- Subject of a report published by the authoritative body concluding that the chemical causes reproductive toxicity

- Otherwise identified as causing reproductive toxicity by the authoritative body in a
document that indicates the identification is a final action.

Formality Criteria:

1 accurate chemical identification

and...

2 one of the following:

- review by advisory committee in public meeting
- public review and comment
- for federal AB published in, e.g., *Federal Register*
- signed by institution head or designee
- adoption as a final rule by body
- set forth in official document used for regulatory purposes

OEHHA Implementation

OEHHA monitors AB publications

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OEHHA document on chemicals appearing to meet 12306 criteria

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Internal review

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Report release. Noticed in *California Regulatory Notice Register (CRNR)*. Posted on web.

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60 day public comment
Public forum

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OEHHA reviews comments

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Notice of intent to list in *CRNR*.
Posted on web.

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30 day public comment
OEHHA reviews objections (30 days)

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Updated Proposition 65 list. Noticed in *CRNR*.
Posted on web.

US ENVIRONMENTAL PROTECTION AGENCY (US EPA)

AUTHORITATIVE BODIES LISTINGS

- *Sole* basis for **15** DARTs listed
- *Partial* basis for **2** DARTs listed

Key Documents for DARTs Listed

- **OFFICE OF RESEARCH AND DEVELOPMENT**

  ◊ Health Effects Assessment
  ◊ Health Issues Assessment
  ◊ Health Assessment Document

- **OFFICE OF PREVENTION, PESTICIDES, AND TOXIC SUBSTANCES**

  ◊ Federal Register notices
  - Additions to the Toxic Release Inventory ("TRI")
  - Toxic Substances Control Act significant new use rules

- **OFFICE OF WATER**

  ◊ Ambient Water Quality Criteria
  ◊ Drinking Water Criteria

US EPA DART GUIDELINES

- *1991 Guidelines for Developmental Toxicity Risk Assessment*

- *1996 Risk Assessment Guidelines for Reproductive Toxicity*

Criteria for minimum evidence to conduct a hazard identification/dose-response evaluation:

- **Human Data**

- **Animal Data**

US EPA (and TRI) Practices and Processes

Processes	US EPA	TRI
Guidance	yes	yes
Research	yes	no[1]
Review and evaluation	yes	yes
Expertise	yes	yes
Wide use and acceptance	yes	yes
Formal public input	yes	yes
Internal peer review	yes	yes
External peer review	yes	no[2]

[1] Many of the studies submitted to US EPA for review and evaluation have been designed and conducted according to specific Agency requirements (i.e., FIFRA guidelines).
[2] The formal public comment period generated technical comments from numerous external technical peer reviewers.

- **<u>Scientific criteria for "as causing reproductive toxicity" (22 CCR 12306(g))</u>**

♦ "as causing reproductive toxicity" means that either:

(1) Studies in humans indicate that there is a causal relationship between the chemical and reproductive toxicity

or

(2) Studies in experimental animals indicate that there are sufficient data … indicating that an association between adverse reproductive effects in humans and the toxic agent in question is biologically plausible.

"Final Statement of Reasons - Chemicals Formally Identified by Authoritative Bodies."

- It is not the intention of the Agency to substitute its scientific judgment for that of the authoritative body.

- The Agency's inquiry will be limited to whether the authoritative body relied on scientific data in an amount sufficient to conclude that the chemical causes reproductive toxicity.

- Because the body is considered authoritative, and the body utilizes the same or substantially the same criteria as set forth in subsection (g), it will be assumed that the data relied upon is scientifically valid.

- The Agency will look to determine whether the authoritative body relied upon animal or human data in an amount sufficient to satisfy the criteria.

o,p'-DDT [Listed May 15, 1998]

- Document cited
  - ◊ *Updated Health Effects Assessment for DDT* (1988). Office of Research and Development, U.S. EPA.

- Basis for Listing - U.S. EPA Conclusions
  - ◊ ". . . DDT has consistently caused a decrease in the reproductive capacity in mice, rats, and dogs."
  - ◊ Specific effects described include changes in gonads, reduced fertility, embryo and fetotoxicity, increased resorption frequency, and premature delivery

- Endpoints Listed
  - ◊ Developmental toxicity
  - ◊ Female reproductive toxicity
  - ◊ Male reproductive toxicity

Endrin [Listed May 15, 1998]

- Documents cited
  - ◊ *Drinking Water Criteria Document for Endrin* (1992). Office of Research and Development, U.S. EPA.
  - ◊ *Ambient Water Quality Criteria for Endrin* (1992). Office of Water Regulations and Standards, U.S. EPA.
- Basis for Listing - U.S. EPA Conclusions
  - ◊ "Endrin has been shown to cause teratogenic effects"
  - ◊ "Prenatal exposure to endrin elicited terata, mortality and/or reduced neonatal weight or weight gain in offspring of hamsters and mice."
  - ◊ Effects observed include fetal death, growth retardation, soft tissue and skeletal malformations, and altered behavior.
- Endpoint Listed
  - ◊ Developmental toxicity

Metham Sodium [Listed May 15, 1998]

- Documents cited
  - ◊ *Proposed Rule: Addition of Certain Chemicals; Toxic Chemical Release Reporting; Community Right to Know* (1994). Federal Register (59 FR 1788). U.S. EPA.
  - ◊ *Final Rule: Addition of Certain Chemicals; Toxic Chemical Release Reporting; Community Right to Know* (1994). Federal Register (59(229) FR 61432). U.S. EPA.
- Basis for Listing - U.S. EPA Conclusions
  - ◊ ". . . there is sufficient evidence for listing metham sodium based on the available developmental toxicity data for this chemical and its metabolite, carbon disulfide."
  - ◊ Effects were manifested as postimplantation loss in rabbits, and as increased variations, retardations, and anomalies in rats.
- Endpoint Listed
  - ◊ Developmental toxicity

Oxadiazon [Listed May 15, 1998]

- Documents cited
  - ◊ *Proposed Rule: Addition of Certain Chemicals; Toxic Chemical Release Reporting; Community Right to Know* (1994). Federal Register (59 FR 1788). U.S. EPA.
  - ◊ *Final Rule: Addition of Certain Chemicals; Toxic Chemical Release Reporting; Community Right to Know* (1994). Federal Register (59(229) FR 61432). U.S. EPA.
- Basis for Listing - U.S. EPA Conclusions
  - ◊ ". . . there is sufficient evidence for listing oxydiazon [sic] based on the available developmental ... toxicity data for this chemical."
  - ◊ Effects were manifested as increased fetal resorptions in rats.
- Endpoint Listed
  - ◊ Developmental toxicity

Vinclozolin [Listed May 15, 1998]

- Documents cited
  - ◊ *Proposed Rule: Addition of Certain Chemicals; Toxic Chemical Release Reporting; Community Right to Know* (1994). Federal Register (59 FR 1788). U.S. EPA.
  - ◊ *Final Rule: Addition of Certain Chemicals; Toxic Chemical Release Reporting; Community Right to Know* (1994). Federal Register (59(229) FR 61432). U.S. EPA.
  - ◊ *Proposed Rule for Pesticide Tolerances for 3-(3,5-Dichlorophenyl)-5-Ethenyl-5-Methyl-2,4-Oxazolidinedione (1988).* Federal Register (53 FR 41209). U.S. EPA.
- Basis for Listing - U.S. EPA Conclusions
  - ◊ ". . . there is sufficient evidence for listing vinclozolin based on the available ... developmental toxicity data for this chemical."
  - ◊ Effects were manifested as pseudohermaphroditism of male offspring, developmental delays, reduced male and female pup weight, and increased stillbirths in rats.
- Endpoint Listed
  - ◊ Developmental toxicity

NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH (NIOSH)

AUTHORITATIVE BODIES LISTINGS

- *Sole* basis for **3** DARTs listed
- *Partial* basis for **2** DARTs listed

Presented by M. Sandy

KEY NIOSH DOCUMENTS FOR DARTs LISTED

◊ *Criteria for a Recommended Standard documents*

◊ *Occupational Safety and Health Guideline*

NIOSH Practices and Processes

Processes	NIOSH
Guidance	yes
Research	yes
Review and evaluation	yes
Expertise	yes
Wide use and acceptance	yes
Formal public input	yes
Internal peer review	yes
External peer review	yes

Ethylene glycol monoethyl ether acetate
[Listed January 1, 1993]

- Document cited
  - ◊ *Criteria for a Recommended Standard: Occupational Exposure to Ethylene Glycol Monoethyl Ether, Ethylene Glycol Monomethyl Ether, and Their Acetates (1991).* National Institute for Occupational Safety and Health.

- Basis for Listing – NIOSH Conclusions
  - ◊ EGEE administered by a variety of routes produced a marked toxic effect on the testes of many animal species. EGEEA has also caused testicular atrophy and depletion of spermatocytes in mice.
  - ◊ Treating pregnant females of various species with EGEE has caused adverse maternal and developmental effects. Embryolethality, visceral and skeletal abnormalities, and reduced fetal weights were observed in the offspring of dams treated with EGEEA.
  - ◊ EGEEA believed to pass through the same metabolic pathway as EGEE after hydrolysis of the ester moiety.
- Endpoints Listed
  - ◊ Developmental toxicity
  - ◊ Male reproductive toxicity

Presented by M. Sandy

NATIONAL TOXICOLOGY PROGRAM (NTP)

AUTHORITATIVE BODIES LISTINGS

- *Sole* basis for **1** DART listed

KEY NTP DOCUMENT FOR DART LISTED

◊ NTP Technical Report

NTP EXPERTISE

- ◊ Recognized leader in testing and evaluation
- ◊ Developed numerous DART tests
- ◊ Center for the Evaluation of Risks to Human Reproduction

NTP Practices and Processes

Processes	NTP
Guidance	yes
Research	yes
Review and evaluation	yes
Expertise	yes
Wide use and acceptance	yes
Formal public input	yes
Internal peer review	yes
External peer review	yes

Nitrofurantoin [Listed April 1, 1991]

- Document cited
  - ◊ *Toxicology and Carcinogenesis Studies of Nitrofurantoin (CAS No. 67-20-9) in F334/N Rats and B6C3F1 Mice (Feed Studies) (1989).* Technical Report Series. National Toxicology Program.

- Basis for Listing – NTP Conclusions
  - ◊ Organs showing toxicity from nitrofurantoin identified in the short-term studies were the testis in male rats and mice and the ovary in female rates and mice.
  - ◊ Lesions observed in the 2-year studies were in the testis in male rates and mice and ovary in female mice.

- Endpoint Listed
  - ◊ Male reproductive toxicity

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER (IARC)

AUTHORITATIVE BODIES LISTINGS

- Thus far, has **not** been a basis for DART listings

POTENTIAL BASES FOR LISTINGS

◊ **IARC** ***Monographs on the Evaluation of Carcinogenic Risks to Humans***

◊ **IARC** ***Handbooks of Cancer Prevention***

IARC GUIDANCE

Evaluation of reproductive and developmental effects

- adequacy of epidemiological studies

- adequacy of animal studies
  - ◊ route of administration
  - ◊ chemical formulation
  - ◊ dosing regimen
  - ◊ treatment duration

IARC Practices and Processes

Processes	IARC
Guidance	yes
Research	yes
Review and evaluation	yes
Expertise	yes
Wide use and acceptance	yes
Formal public input	no
Internal peer review	yes
External peer review	no

US FOOD AND DRUG ADMINISTRATION

AUTHORITATIVE BODIES LISTINGS

- Thus far, has not been a basis for DART listings.
- However, numerous DARTs have been listed based upon the FDA having formally required the chemical to be labeled or identified.

POTENTIAL BASES FOR LISTINGS

◊ *Federal Register* notices

FDA Practices and Processes

Processes	FDA
Guidance	yes
Research	yes
Review and evaluation	yes
Expertise	yes
Wide use and acceptance	yes
Formal public input	yes
Internal peer review	yes
External peer review	yes

US AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY

◊ *Toxicological Profiles*

ATSDR

- Guidelines developed by the ATSDR and the U.S. EPA, published in the Federal Register in 1987.

- ATSDR identifies plausible non-cancer outcomes based on:

    - ♦ plausible adverse health effects in humans.

    - ♦ health outcomes identified in animals that can reasonably be expected to occur in humans.

ATSDR

- **Working Procedures**

  ⇒*Toxicological Profiles* generally developed by external contractors, undergo several levels of internal review before adoption.

- **Peer Review**

  ⇒*Toxicological Profiles* undergo external peer review by a non-governmental panel of scientists convened for that purpose.

INTERNATIONAL PROGRAM ON CHEMICAL SAFETY

◊ *Environmental Health Criteria*

◊ *Concise International Chemical Assessment Documents*

◊ *Health and Safety Guides*

IPCS

- *Principles and Methods for Evaluating the Toxicity of Chemicals, Part 1. EHC 6, 1978*

- *Principles for Evaluating Health Risks to Progeny Associated with Exposure to Chemicals During Pregnancy. EHC 30, 1984*

- *Principles for Evaluating Health Risks from Chemicals during Infancy and Early Childhood: The Need for a Special Approach. EHC 59, 1986*

IPCS

- **Working Procedures**

  ⇒Documents devised and drafted by international teams of scientists

- **Peer Review**

  ⇒Documents reviewed by international teams of scientists

HEALTH CANADA

- **CANADIAN ENVIRONMENTAL PROTECTION ACT**

  ◊ *Priority Substances List Assessment Reports / Supporting Documents*

- ***1994 Human Health Risk Assessment for Priority Substances***

HEALTH CANADA

- **Working Procedures**

  ⇒Assessment reports and supporting documents prepared by the Environmental Substances Division of Health Canada.

  ⇒Approval by an interdirectorate committee of the Health Protection Branch of Health Canada.

- **Peer Review**

◊ External peer review by an international group of expert scientists.